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Correlation of elevated lamotrigine and levetiracetam serum/plasma levels with toxicity: A long-term retrospective review at an academic medical center

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ABSTRACT

Lamotrigine and levetiracetam are widely used second-generation anti-epileptic drugs. Existing literature indicates that overdose of either drug is typically benign, but neurologic and cardiac toxicity can occur in some cases. In this retrospective study, we analyzed a large dataset of serum/plasma drug levels for lamotrigine and levetiracetam. The data covered 1,930 unique patients (5,046 levels) for lamotrigine and 2,451 patients (4,359 levels) for levetiracetam. We performed detailed chart review on all patients with one or more lamotrigine levels greater than 14.0 mg/L (293 unique patients) and all patients with one or more levetiracetam levels of 80 mg/L or higher (106 unique patients). No deaths directly attributable to lamotrigine or levetiracetam toxicity were reported. For cases with lamotrigine levels greater than 14.0 mg/L, the majority of patients were asymptomatic (55.3 %, n = 162). The most common presenting symptoms were ataxia (14.3 %, n = 42), seizures (14.0 %, n = 41), dizziness (11.9 %, n = 35), and altered mental status (11.6 %, n = 34). There were 12 overdoses (11 intentional) involving lamotrigine, all of which presented with either altered mental status (n = 8) or seizures (n = 4). The highest estimated dose reportedly ingested was 20 g. Cardiac toxicity was observed in two cases involving intentional overdose of lamotrigine. For patients with levetiracetam serum/plasma levels of 80 mg/L or higher, 48 patients (45.3 %) were asymptomatic. Symptomatic patients most commonly presented with seizures (31.1 %, n = 33) and altered mental status (15.1 %, n = 16), and none showed cardiac symptoms. There were only two cases involving intentional levetiracetam overdose, one of which presented with altered mental status after ingestion of 45 g and the other asymptomatic after ingestion of 6 g. Overall, our data is consistent with previous investigations that lamotrigine and levetiracetam toxicity most typically presents with neurologic symptoms and rarely cardiac arrhythmias. Approximately half of the patients with elevated lamotrigine or levetiracetam drug levels are asymptomatic.

1. Introduction

Therapeutic drug monitoring (TDM) of anti-epileptic drugs (AED) has been used to guide seizure management and monitor medication adherence [1]. Dosing requirements for AEDs may fluctuate depending on type of epilepsy, age, pregnancy, concomitant drug therapy, and comorbidities affecting pharmacokinetics [2–5]. With dosing adjustments and changes in clinical status, monitoring for toxicity is imperative. Toxicity thresholds vary by AED. Complex pharmacokinetics, including the phenomenon of 'auto-induction' of metabolism shown by some AEDs, can cause individual variation in drug levels. Drug-drug interactions can alter metabolism, and clinical conditions such as renal insufficiency and pregnancy can affect AED clearance [3,4]. With such variables, monitoring for toxicity should include consideration of individual risk factors.

TDM has been commonly used for "first-generation" AEDs such as carbamazepine, phenobarbital, phenytoin, and valproic acid [1,2]. These medications have had decades of clinical use and generally have complicated pharmacokinetics and a high risk for toxicity if blood levels are too high. In the past 25 years, over 20 novel AEDs, sometimes referred to as second-and third-generation AEDs, have gained regulatory approval in the United States (US) and in other countries [6]. While the newer AEDs tend to have broader therapeutic ranges, more predictable pharmacokinetics, and lower risk of toxicity compared to the

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first-generation AEDs, some have attributes that make TDM clinically useful [1,2]. The present study focuses on two widely used second-generation AEDs, lamotrigine and levetiracetam.

Lamotrigine is a phenyltriazine compound approved for use in the US in 1994. Lamotrigine is currently approved for the treatment of seizures and bipolar disorder [7,8]. It inhibits voltage-gated sodium and high-voltage-activated calcium channels, and inhibits reuptake of serotonin, norepinephrine, and dopamine. Multiple factors favor clinical use of TDM for lamotrigine [1,2]. Clearance of lamotrigine is higher in children and much higher in pregnant women compared to non-pregnant women and adult men [9]. Liver metabolism plays a key role in the elimination of lamotrigine, with potential for drug-drug interactions with liver enzyme inducers (e.g., carbamazepine, estrogen-containing contraceptives, phenobarbital, phenytoin) and inhibitors (especially valproic acid) [3,4]. Lamotrigine also shows the property of auto-induction of metabolism so that dose adjustments are needed to maintain therapeutic levels. In published case series and retrospective reviews, lamotrigine overdose is typically benign, but serious toxicity including death and cardiac arrhythmias have been reported in some cases [10–17]. Adverse effects have been reported to increase significantly when serum/plasma levels exceed 14 milligrams per liter (mg/L) but vary by individual [2]. A reference range of 3.0–14.0 mg/L has been proposed for treatment of seizures [18]. Lamotrigine serum/plasma levels can be measured by either chromatographic-based methods (e.g., liquid chromatography/mass spectrometry) or enzyme immunoassays (EIAs) that can run on clinical laboratory chemistry analyzers [2].

Levetiracetam inhibits high-voltage activated calcium channels, and was approved for use in the US in 1999 for treatment of seizures [19,20]. Levetiracetam is commonly dosed orally for chronic management of seizures; however, there are also parenteral formulations that can be used for acute management of seizures such as in status epilepticus [21]. The pharmacokinetics of levetiracetam are generally predictable, with negligible liver metabolism and nearly 100 % of the drug excreted by the kidneys. Dose adjustments are required for those with renal insufficiency [3,4]. Overdoses are typically well tolerated, with the majority of patients remaining asymptomatic [17,22–28]. The proposed reference range is 12–46 mg/L [19]. Similar to lamotrigine, levetiracetam serum/plasma levels can be assessed by either chromatographic-based methods or EIAs [2]. Analytical methodology for both lamotrigine and levetiracetam generally correlate well for both patient samples and proficiency testing [29–33].

The widespread clinical use of lamotrigine and levetiracetam increase the probability of accidental or intentional overdose. With the increased use of TDM for these drugs, more data is available to ascertain correlations of serum/plasma levels with clinical toxicity. In this study, we retrospectively reviewed cases of elevated lamotrigine and levetiracetam serum/plasma levels in a mixed cohort of adult and pediatric patients treated at a single academic medical center. Goals of this study were to describe clinical manifestations and outcomes in patients with elevated lamotrigine and levetiracetam levels.

2. Methods

2.1. Design and setting

This was a retrospective study of all patients (pediatric and adult) who had a lamotrigine or levetiracetam serum/plasma level performed at the University of Iowa Hospitals and Clinics (UIHC) between August 1, 1996 through November 15, 2018 for lamotrigine and between January 1, 2005 and November 15, 2018 for levetiracetam. UIHC is the state of Iowa's only academic medical center, and performs laboratory testing for the adult hospital, outpatient clinics, emergency department (ED), and children's hospital. Inpatient and outpatient patient care areas were included. Inpatient included both UIHC and the adjacent University of Iowa Stead Family Children's Hospital. Outpatient included main campus clinics, satellite clinics, and the ED. This study received institutional review board approval from the University of Iowa Institutional Review Board (protocol # 201812703). UIHC uses Epic (Epic, Inc.) as the electronic medical record (EMR). As described in previous studies [34], Epic Reporting Workbench was used as a reporting tool to retrieve data based on specific query parameters. In particular, searches retrieved all lamotrigine and levetiracetam serum/plasma levels available within the retrospective analysis timeframe.

2.2. Data

Demographic data collected included gender (male or female), age at time of laboratory testing, and clinic or hospital location. A high (potentially toxic) lamotrigine level was defined as greater than 14.0 mg/L. This threshold was chosen based on the proposed reference range of 3.0–14.0 mg/L, and published literature showing increased risk of toxicity above 14.0 mg/L [1,2,18]. A high (potentially toxic) levetiracetam level was defined as 80 mg/L or higher. A reference range of 12–46 mg/L has been proposed for levetiracetam [19]. Unlike lamotrigine, a toxic serum/plasma level threshold for levetiracetam has not been defined. We chose 80 mg/L or higher to provide a large but manageable cohort of elevated levetiracetam levels for detailed chart review. For patients with high lamotrigine and levetiracetam levels, chart review was performed to determine indication for drug level, timing of level, and medication outcome (i.e., hold dose, discontinue drug, increase dose, or decrease dose). Indication for lamotrigine or levetiracetam TDM was subcategorized as documented overdose (intentional or accidental), routine check not in pregnancy, routine check in pregnancy or post-partum period ('obstetric'), clinical evidence of seizures, possible symptoms of drug toxicity (not associated with known overdose), or unknown. The unknown category includes situations where the drug level was obtained as a laboratory only visit, not associated with a clinic encounter, or where no signs or symptoms were documented. In the retrospective timeframe of the study, pharmacogenetic testing for genetic variants or drug-related tissue/organ sampling related to lamotrigine or levetiracetam was not utilized at the medical center.

Timing of the TDM was subcategorized as peak, trough, other specific timing, and random/unknown. Designations of peak, trough, or other specific timing were used only if there was specific documentation that these timings were used for purpose of pharmacokinetic interpretation. As described below in the Results, the vast majority of timings were random or unknown, reflecting an absence of any specialized pharmacokinetic protocol in the medical center for dosing of lamotrigine or levetiracetam. Medication outcome referred to actions taken based on serum/plasma level and was subcategorized as any measures that lowered dose (decrease maintenance dose amount, hold one or more doses, or discontinued drug altogether), maintained dose, increased dose amount, or unknown. Current use of valproic acid in patients with lamotrigine levels greater than 14.0 mg/L was extracted by chart review, as the drug-drug interaction between valproic acid (a liver enzyme inhibitor) and lamotrigine can lead to high lamotrigine serum/plasma levels as explained above.

Chart review for symptomatology focused on clinical signs and symptoms documented in the patient medical record that may have been associated with drug toxicity. This is a similar approach to other retrospective investigations of lamotrigine and levetiracetam toxicity [10,14,35]. Clinical signs and symptoms were considered as possibly representative of drug toxicity if they were distinct from baseline level of function (or at least a worsening of previous function) and causally connected to drug exposure. For some symptoms, especially seizures, it is difficult to ascertain whether the symptoms are related to the underlying medical disorder or related to drug toxicity or both. If documented in the medical record, neurologic examination by the clinical team was used for assessment of neurological signs and symptoms. "Altered mental status" was defined as a general change in brain function

from the baseline for the patient, encompassing symptoms such as amnesia, confusion, loss of alertness, disorientation, and disruptions in perception. "Ataxia" was defined as a lack of muscle control or difficulty in the coordination of voluntary movements, impacting tasks such as walking or picking up objects. A combined category for "tremors/twitches/jerks" included unintentional and repetitive muscle movements involving one or more parts of the body. This category encompassed effects that were distinct from the baseline seizure disorder being treated by lamotrigine or levetiracetam. Given that patients presenting with toxicity were seen in a variety of clinical settings, there was significant variability in documentation of these type of muscle movements. "Muscle weakness" (reduced muscle strength) was defined by inability to produce normal muscle contraction despite full effort. A patient episode was considered "asymptomatic" if a documented medical evaluation of the patient did not identify any symptoms or signs different from baseline that could be associated with drug toxicity. As described above, there are cases where clinical signs and symptoms were unknown due to lack of documentation, a situation that most commonly occurred when patients had routine lamotrigine or levetiracetam serum/drug levels measured outside of a clinic visit or inpatient hospital encounter.

Pediatric patients were defined as less than 18 years old and were analyzed as a subset of the total cohort. Cases of intentional overdose and death were reviewed in detail for underlying causes and outcome. Descriptive statistics (mean, standard deviation, median, proportions) were used to summarize the data (Microsoft Excel).

2.3. Analytical methodology

In the retrospective timeframe, lamotrigine and levetiracetam serum/plasma levels were determined at a commercial reference laboratory (ARUP Laboratories, Salt Lake City, UT, USA) until July 8, 2011. Starting July 9, 2011, lamotrigine and levetiracetam were analyzed at UIHC by EIA (ARK Diagnostics Lamotrigine Assay and Levetiracetam Assay, respectively) on Roche Diagnostics c502 analyzers. The ARK Lamotrigine Assay is a homogeneous immunoassay utilizing competition between lamotrigine in the patient specimen and lamotrigine labeled with a bacterial glucose-6-phosphate dehydrogenase (G6PDH) enzyme in the reagent ('lamotrigine/G6PDH conjugate') for binding to rabbit polyclonal antibodies to lamotrigine [31,36]. If there is little or no lamotrigine in the patient specimen, the reagent anti-lamotrigine antibodies will predominantly bind to the lamotrigine/G6PDH conjugate. By steric hindrance, this antibody binding prevents the G6PDH enzyme in the lamotrigine/G6PDH conjugate from converting nicotinamide adenine dinucleotide (NAD) to NADH, with the amount of NADH formation measured spectrophotometrically as a rate of change of absorption. The rate of absorption change is then used to determine the concentration of lamotrigine. In the presence of higher concentrations of lamotrigine in the patient specimen, the polyclonal antibodies will predominantly bind to the lamotrigine in the specimen, allowing for more of the G6PDH in the lamotrigine/G6PDH conjugate to convert NAD to NADH. The lower limit of quantitation for the lamotrigine assay is 0.85 mg/L. The lamotrigine assay shows minimal cross-reactivity with several characterized lamotrigine metabolites including lamotrigine-2-*N*-glucuronide (< 3.0 % cross-reactivity), lamotrigine-2-*N*-methyl (< 0.2 % cross-reactivity), and lamotrigine-2-*N*-oxide (< 4.0 % cross-reactivity). These compounds are typically found at very low concentrations relative to the parent drug in human plasma and thus likely have minimal impact on determination of lamotrigine serum/plasma concentrations with the EIA [37,38]. The only other drug cross-reactivity reported for the lamotrigine assay is trimethoprim, with less than 4.5 % cross-reactivity [36].

The basic principal for the ARK Levetiracetam Assay is the same as for the lamotrigine assay, except that the reagent utilizes rabbit polyclonal antibodies to levetiracetam and a levetiracetam/G6PDH conjugate [30,39]. The lower limit of quantitation for the levetiracetam assay is 2.0 mg/L. Levetiracetam has a single major metabolite, 2-pyrrolidone-*N*-butyric acid (also referred to as ucb L057 or simply L057) [38]. This metabolite has less than 1.5 % cross-reactivity with the levetiracetam assay and thus likely has minimal impact on determination of levetiracetam serum/plasma concentrations [39].

3. Results

3.1. Subject demographics – total cohort

For lamotrigine, a total of 1,930 patients had one or more serum/plasma levels checked. There were more females (55.3 %, n = 1,068) than males (44.7 %, n = 862). The mean age was 39.3 years old (SD 17.2, median 37.7) with ages ranging from newborn to greater than 89 years old. In total, 5,046 drug levels were obtained, with a mean of 2.6 levels per patient (Table 1). For levetiracetam, 2,451 patients had one or more serum/plasma levels checked, with equal percentage of females (50.0 %, n = 1,225) and males (50.0 %, n = 1,226). The mean age was 42.1 years old (SD 21.8, median 42.0) with ages ranging from newborn to greater than 89 years old. The total number of drug levels was 4,359, with a mean of 1.8 levels per patient (Table 1). A total of 261 patients had both lamotrigine and levetiracetam drug levels performed in the retrospective timeframe (in many cases at different timepoints as medication regimens were revised). Thus, the total dataset is 9,405 samples originating from 4,120 unique patients.

Table 1
Demographics of Patients with Lamotrigine and Levetiracetam Serum/Plasma Drug Levels.

	Lamotrigine		Levetiracetam	
	All patients (n = 1930)	Patients with level > 14 mg/L (n = 293)	All patients (n = 2451)	Patients with level ≥ 80 mg/L (n = 106)
Gender				
Female	1068 (55.3 %)	163 (55.6 %)	1225 (50.0 %)	33 (31.1 %)
Male	862 (44.7 %)	130 (44.4 %)	1226 (50.0 %)	73 (68.9 %)
Age in years				
Mean (standard deviation)	39.3 (17.2)	37.8 (16.2)	42.1 (21.8)	47.5 (21.5)
Median age	37.7	35.6	42.0	53.5
Minimum age	Newborn	2	Newborn	0.8
Maximum age	> 89	77	> 89	> 89
Number of total drug levels[a]	(n = 5046)	(n = 597)	(n = 4359)	(n = 134)
Female	2678 (53.1 %)	326 (54.6 %)	2262 (51.9 %)	88 (65.7 %)
Male	2368 (46.9 %)	271 (45.4 %)	2097 (48.1 %)	46 (34.3 %)
Mean number of drug levels per patient	2.6		1.8	
Number of patients with 2 or more high levels during same inpatient encounter[b]	85		14	

[a] The total number of drug levels obtained exceeds the total number of patients as patients may have had more than 1 level checked during the study time period.

[b] High levels were defined as > 14.0 mg/L for lamotrigine and ≥ 80.0 mg/L for levetiracetam.

3.2. Patients with serum/plasma lamotrigine level greater than 14.0 mg/L

Of the 1,930 patients in the lamotrigine cohort, 15.2 % (n = 293) had at least 1 serum/plasma level greater than 14.0 mg/L. Within this high lamotrigine group, 55.6 % (n = 163) were female and 44.4 % (n = 130) were male. The mean age was 37.8 years old (SD 16.2, median 35.6), with ages ranging from 2 to 77 years old. Of the total number of lamotrigine levels, 11.8 % (n = 597) were greater than 14.0 mg/L. Eighty-five patients had two or more levels greater than 14.0 mg/L during the same hospital encounter (Table 1). Of the 293 total patients with a level greater than 14.0 mg/L, 18 (6.1 %) patients were concurrently taking valproic acid. Thirty-eight (6.4 %) of all lamotrigine levels greater than 14.0 mg/L (n = 597) involved concurrent use of valproic acid.

In the group with high lamotrigine levels, the most common documented indications for obtaining the lamotrigine serum/plasma level were routine check not in pregnancy and possible symptoms of drug toxicity at 47.9 % (n = 286) and 33.5 % (n = 200), respectively. The reason was unknown in 8.5 % (n = 51) of levels obtained. For 96.8 % (n = 578) of levels, the timing was random or unknown. For levels greater than 14.0 mg/L, a dosing adjustment to decrease maintenance dose, temporarily hold doses(s), or discontinue drug occurred 28.8 % (n = 172) of the time. Dosing was increased following 4.5 % (n = 27) of levels and maintained for 45.7 % (n = 273) levels (Table 2). The majority of patients were asymptomatic at time of lamotrigine drug level (55.3 %, n = 162). Of symptomatic patients, the most common presentations were ataxia (14.3 %, n = 42), seizures (14.0 %, n = 41), dizziness (11.9 %, n = 35), and altered mental status (11.6 %, n = 34) (Table 3). Psychosis was documented in 4 patients (1.4 %).

3.3. Patients with serum/plasma levetiracetam levels of 80 mg/L or higher

Of the 2,451 total patients who had levetiracetam serum/plasma levels determined, 4.3 % (n = 106) had a level of 80 mg/L or higher, with more males (68.9 %, n = 73) than females (31.1 %, n = 33). The mean age was 47.5 years old (SD 21.5, median 53.5), with ages ranging from 0.8 to greater than 89 years old. Overall, 3.1 % (n = 134) of all levetiracetam levels were 80 mg/L or higher. Fourteen patients had two or more levels 80 mg/L or higher during the same hospital encounter (Table 1).

For the patients with high levetiracetam levels, the most common indications for obtaining the level was routine check not in pregnancy and possible symptoms of drug toxicity at 40.3 % (n = 54) and 43.3 % (n = 58), respectively. For 11.2 % (n = 15) levels, the indication for TDM was unknown. The timing of the level was random or unknown for 98.5 % (n = 132) of drug levels. In response to the elevated drug level, the medication dose was maintained for 38.1 % (n = 51) and increased for 1.5 % (n = 2). The maintenance dose was decreased, temporarily held, or discontinued following 16.4 % (n = 22) of levels. The outcome for medication dosing was unknown for 44.0 % (n = 59) of levels (Table 2). Forty-eight (45.3 %) of patients were asymptomatic at time of drug level of 80 mg/L or higher. Symptomatic patients most commonly presented with seizures and altered mental status at 31.1 % (n = 33) and 15.1 % (n = 16), respectively (Table 3).

Table 2
Indication, Timing, and Outcome of High Lamotrigine and Levetiracetam Serum/Plasma Drug Levels.

	Lamotrigine level > 14 mg/L (n = 597) n (%)	Levetiracetam level ≥ 80 mg/L (n = 134) n (%)
Indication for Ordering Specific Drug Level		
Documented overdose (intentional or accidental)	34 (5.7 %)	3 (2.2 %)
Routine check (not related to pregnancy)	286 (47.9 %)	54 (40.3 %)
Routine check pregnancy or post-partum	10 (1.7 %)	0 (0.0 %)
Seizures	16 (2.7 %)	4 (3.0 %)
Possible symptoms of drug toxicity	200 (33.5 %)	58 (43.3 %)
Unknown	51 (8.5 %)	15 (11.2 %)
Timing of level		
Peak	6 (1.0 %)	1 (0.7 %)
Trough	7 (1.2 %)	0 (0.0 %)
Other specific timing	6 (1.0 %)	1 (0.7 %)
Random/unknown	578 (96.8 %)	132 (98.5 %)
Changes in Drug Dosing		
Decreased, temporarily held, or discontinued maintenance dose	172 (28.8 %)	22 (16.4 %)
Maintained maintenance dose	273 (45.7 %)	51 (38.1 %)
Increased maintenance dose	27 (4.5 %)	2 (1.5 %)
Unknown	125 (20.9 %)	59 (44.0 %)

Table 3
Clinical Symptoms for Patients with Elevated Lamotrigine and Levetiracetam Drug Levels[a].

Presenting Signs and Symptoms	Patients with Lamotrigine level > 14 mg/L (n = 293) n (%)	Patients with Levetiracetam level ≥ 80 mg/L (n = 106) n (%)
Agitation/aggression	10 (3.4 %)	5 (4.7 %)
Altered mental status[b]	34 (11.6 %)	16 (15.1 %)
Asymptomatic	162 (55.3 %)	48 (45.3 %)
Ataxia[b]	42 (14.3 %)	2 (1.9 %)
Cardiac	2 (0.7 %)	0 (0.0 %)
Dizziness	35 (11.9 %)	2 (1.9 %)
Dysarthria	2 (0.7 %)	0 (0.0 %)
Fatigue	7 (2.4 %)	1 (0.9 %)
Headache	5 (1.7 %)	1 (0.9 %)
Known ingestion	6 (2.0 %)	2 (1.9 %)
Muscle weakness	5 (1.7 %)	3 (2.8 %)
Nausea/vomiting	15 (5.1 %)	0 (0.0 %)
Nystagmus	3 (1.0 %)	1 (0.9 %)
Paranoia	2 (0.7 %)	0 (0.0 %)
Psychosis[b]	4 (1.4 %)	0 (0.0 %)
Respiratory distress	2 (0.7 %)	0 (0.0 %)
Seizures	41 (14.0 %)	33 (31.1 %)
Serotonin syndrome	3 (1.0 %)	0 (0.0 %)
Tremors, twitches, or jerks[b]	15 (5.1 %)	0 (0.0 %)
Unknown (presence or absence of symptoms not documented)	23 (7.8 %)	2 (1.9 %)
Vision changes	15 (5.1 %)	0 (0.0 %)
Miscellaneous (n = 1 each only for lamotrigine)	Coma, drooling, dry mouth, dysarthria, night sweats, paresthesia, weight loss	None

[a] The table summarizes the main two clinical symptoms and signs (if present) documented at time that drug level was obtained.

[b] "Altered mental status" was defined as a general change in brain function from the baseline for the patient, encompassing symptoms such as amnesia, confusion, loss of alertness, disorientation, and disruptions in perception. "Ataxia" describes a lack of muscle control or coordination of voluntary movements, such as walking or picking up objects. “Muscle weakness" (reduced muscle strength) was defined by inability to produce normal muscle contraction despite full effort. “Psychosis” referred to situations where patient showed psychiatric symptoms with loss of touch with reality that seemed causally connected with drug toxicity. “Tremors, twitches, or jerks” were unintentional muscle movements involving one or more parts of the body and classified as a single combined group given widely varying documentation of symptoms in the electronic medical record even though different mechanisms likely underlie these effects. This category encompasses cases where these effects seem distinct from the baseline seizure disorder.

3.4. Pediatric patients (less than 18 years old)

For lamotrigine, a total of 165 pediatric patients (8.5 % of the total

cohort) were included, with 24 of the 152 (15.8 %) pediatric patients having a level greater than 14.0 mg/L. In pediatric patients, 335 drug levels (6.6 % of the total lamotrigine levels for all patients) were obtained, and 49 (14.6 % of the pediatric levels) were greater than 14.0 mg/L. For pediatric patients with levels greater than 14.0 mg/L, two patients were taking concurrent valproic acid, with a total of 5 levels drawn.

For levetiracetam, 303 pediatric patients (12.4 % of the overall cohort) were included with 8 of the 303 (2.6 %) pediatric patients having a level of 80 mg/L or higher. For drug levels, 536 (12.3 % of the total levetiracetam levels for all patients) levels were obtained in pediatric patients, and 12 of 556 pediatric levels (2.2 %) were 80 mg/L or higher.

3.5. Obstetric patients

Obstetric patients (encompassing both pregnant and post-partum women) were identified based upon the clinical location associated with the order to obtain a drug level. Forty-two obstetric patients (2.2 % of overall patients) had lamotrigine levels obtained, for a total of 107 (2.1 % of overall) drug levels. Two (4.8 %) of the obstetric patients had one or more lamotrigine levels greater than 14.0 mg/L during an obstetric-related encounter, comprising 6 total levels. For levetiracetam, 66 obstetric patients (2.7 % of overall patients) were included, and 76 (1.7 % of overall) individual drug levels were obtained. There were no obstetric patients with levetiracetam levels of 80 mg/L or higher.

3.6. Cases of overdose

Known lamotrigine overdoses resulting in levels greater than 14.0 mg/L occurred in 12 patients with a combined 34 drug levels. No fatalities resulted. The overdose was intentional in 11 of the 12 cases. All presented with either seizures (n = 4) or altered mental status (n = 8). Arrythmias were noted in two cases described below. Co-ingestions occurred in three cases, with two involving quetiapine and one involving phenytoin. The highest lamotrigine level per patient ranged from 14.4 to 80.7 mg/L. For three cases with documentation of the ingested lamotrigine dose, the estimated amount ingested was 3.5, 10, and 20 g, respectively.

Two cases of cardiac toxicity occurred in intentional lamotrigine overdose. Right bundle branch block and intraventricular conduction delay developed in a teenager who reportedly ingested 3.5 g of lamotrigine with a peak level of 15.6 mg/L obtained 24 h after ingestion. The other case involved a young adult who developed electrocardiogram abnormalities including left axis deviation, borderline prolonged QT interval, and T wave abnormalities after reportedly ingesting 10 g of lamotrigine, with a peak level of 80.7 mg/L obtained approximately 12 h after ingestion. Both recovered fully with complete resolution of cardiac changes.

Known levetiracetam overdoses was documented in two patients (3 drug levels) who had levetiracetam serum/plasma levels of 80 mg/L or higher. Neither resulted in fatality. Both cases were from intentional ingestion and had serum/plasma levels exceeding 100 mg/L. One patient presented with altered mental status and had reportedly ingested 45 g of levetiracetam. The other patient was asymptomatic and had reportedly ingested 6 g of levetiracetam and 2.5 g of diphenhydramine.

3.7. Mortality associated with high lamotrigine and levetiracetam levels

We also reviewed patient deaths that occurred on same inpatient encounter as a high lamotrigine or levetiracetam level. There was one death in the cohort of patients with a lamotrigine level greater than 14.0 mg/L. This death was in a 76 year old male and attributed to aspiration pneumonia and septic shock. The death was considered unrelated to lamotrigine. There were 5 deaths that occurred during the same inpatient admission in which there was a levetiracetam level of 80 mg/L or higher. All death causes in these cases were considered unrelated to levetiracetam toxicity and related to disease conditions that pre-dated the levetiracetam dosing: sepsis of unknown etiology in a 73 year old female; sepsis secondary to acute mesenteric ischemia and small bowel necrosis in a 71 year old female; encephalopathy and respiratory failure in a 49 year old female; sepsis related to soft tissue infection in a 47 year old female recovering from severe burns; and brain toxoplasmosis in a 45 year old male with immunocompromised state from acute myeloid leukemia and related therapy. No pediatric deaths occurred during hospital encounters with elevated lamotrigine or levetiracetam levels.

4. Discussion

Our retrospective study at an academic medical center covered 22 years for lamotrigine (1996–2018) and 13 years (2005–2018) for levetiracetam, with detailed chart review of all patients with a lamotrigine serum/plasma level greater than 14.0 mg/L (upper limit of proposed reference range) and all patients with a levetiracetam serum/plasma level of 80 mg/L or higher. Across the retrospective timeframe, no deaths directly attributable to elevated serum/plasma levels of lamotrigine or levetiracetam occurred. In our study, over half of the patients with lamotrigine levels greater than 14.0 mg/L were asymptomatic. For levetiracetam, approximately 45 % of patients with serum/plasma levels of 80 mg/L or higher were asymptomatic despite serum levels nearly twice or more the proposed upper reference range limit of 46 mg/L.

Our overall findings and adverse events are similar to what has been described in the literature for lamotrigine toxicity [10–17], although we did not have any fatalities attributed to lamotrigine. Lamotrigine toxicity primarily affects the neurologic and cardiac systems. Central nervous system (CNS) and cardiac manifestations are secondary to lamotrigine's inhibition of voltage-sensitive sodium channels responsible for the initiation and propagation of action potentials in nervous and muscle cells [40]. In our study, CNS symptoms predominated with altered mental status being the most common. Cardiac toxicity was infrequent, occurring in only two patients who intentionally overdosed on lamotrigine. Lamotrigine clearance is higher in children than adults, a factor which may lessen risk of toxicity in children [9]. Literature reports of lamotrigine toxicity in pediatric patients is sparse, and most reported cases involved infants and toddlers after an acute ingestion [10,14,41,42]. Alyahya et al. described 12 pediatric patients with acute lamotrigine overdose ranging in age from 12 days to 4 years old [10]. Eight developed seizures, including two with status epilepticus with serum drug levels ranging from 3.8–35 mg/L. One developed tachycardia and right bundle branch block with a serum level of 28.4 mg/dL. No deaths occurred.

Our findings with levetiracetam also largely match the reported literature [17,22–28]. In our study, approximately 45 % of patients with a levetiracetam serum/plasma level of 80 mg/L or higher were asymptomatic. Case series have reported that the majority of levetiracetam ingestions involved mild or no symptoms [17,23,35,43], including a review of 222 single agent ingestions involving adults and children reported to American Poison Control Centers, with only one levetiracetam ingestion classified as major (serious) outcome and three as moderate outcomes [23].

Prior publications have reported altered mental status to be the primary manifestation of levetiracetam toxicity [17,23]; in contrast, symptomatic patients in our cohort most commonly presented with seizures (approximately one-third of those with levels of 80 mg/L or higher) followed by altered mental status. One explanation for our findings may be that the presenting seizure was the result of the patient's underlying epilepsy or medical condition rather than drug toxicity, and the serum/plasma drug level was obtained to guide additional management and/or assess compliance. This would be a likely scenario for at least a subset of our patients with epilepsy that has been difficult to treat, including refractory epilepsy associated with syndromes such as Lennox-Gestaut. Alternatively, a paradoxical effect with increase in

seizure frequency has been described in some epileptic children and adults taking higher doses of levetiracetam [44]. No patients in our levetiracetam cohort developed cardiotoxicity, consistent with published data indicating low incidence of cardiac adverse effects related to levetiracetam toxicity [44].

TDM may be clinically useful for lamotrigine based upon its complex pharmacokinetics and multiple factors that affect clearance, including drug-drug interactions and pregnancy [1,2]. For levetiracetam, with its predictable pharmacokinetics and nearly 100 % renal excretion, TDM is most useful for guiding dosing adjustments for renal impairment and pregnancy [1,2,45]. For our patients with an elevated lamotrigine or levetiracetam level, a common indication for TDM was routine check in 47.9 % and 40.3 % cases, respectively. Symptom-driven testing occurred in 33.5 % and 43.3 % of cases for lamotrigine and levetiracetam, respectively. The levetiracetam cut-off for detailed chart review (80 mg/L) that we adopted in our study was nearly double the upper reference range limit for management of seizures (46 mg/L); yet, even at these high levetiracetam levels, less than 20 % of elevated levels resulted in a dosing adjustment. This is consistent with limited clinical application of TDM for levetiracetam. For those with an elevated lamotrigine level, 28.8 % resulted in dose adjustments that either temporarily lowered doses or reduced maintenance dose. Similarly, Hirsch et al. reported that 30 % of patients taking lamotrigine required a dose adjustment due to adverse effects, with a sharp increase in dose changes for patients with lamotrigine levels greater than 15 mg/L [46]. There is limited published literature on dosing and toxicity of lamotrigine and levetiracetam in patient subgroups such as those with another serious medical illness (e.g., sepsis, pneumonia, stroke) or at extremes of age [27,47,48]. There is also opportunity for more study of gender-based differences, including pregnancy, on the pharmacokinetics and pharmacodynamics of lamotrigine and levetiracetam [45,47–49].

Limitations of our study include that it was performed at a single academic medical center in the Midwest. Some data was unknown for indication, timing, and medication outcome for serum/plasma levels of lamotrigine and levetiracetam. Manual chart review was dependent on provider documentation in the electronic medical record. In our study, we evaluated serum/plasma levels rather than medication dosage in patients who had a level obtained. Many publications to date have looked at acute ingestions and medication dose ingested and thus our data provide a complement to that literature. Lastly, our study relied on lamotrigine or levetiracetam serum/drug levels and clinical observations, as these were the tools used at the medical center. Future directions to improve efficacy, safety, and identification of toxicity include the use of pharmacogenetic testing (especially for drug-metabolizing enzymes), tissue/organ sampling, and more detailed biomarker analysis including proteomics. There is ongoing research in these realms for lamotrigine and levetiracetam [48,50,51].

5. Conclusion

In this large mixed cohort of adult and pediatric patients with elevated lamotrigine or levetiracetam serum/plasma levels, over half were asymptomatic. Cardiac toxicity was rare, and no deaths occurred as a result of toxicity. Seizures were common in both groups, an unexpected finding for levetiracetam toxicity causing speculation that the underlying medical condition rather than toxicity was to blame. TDM was often performed for surveillance, and infrequently resulted in a medication adjustment.

CRediT authorship contribution statement

Kelly E. Wood: Formal analysis, Conceptualization, Writing - original draft, Writing - review & editing, Methodology. **Kendra L. Palmer:** Formal analysis, Writing - original draft, Writing - review & editing. **Matthew D. Krasowski:** Formal analysis, Conceptualization, Writing - original draft, Writing - review & editing, Methodology, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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